

201-15835A

TEST PLAN FOR ISOCYANIC ACID, m-PHENYLENEDIISOPROPYLIDENE  
(CAS# 2778-42-9) (TMXDI)

OVERVIEW

Cytec Industries Inc. agreed to sponsor isocyanic acid, m-phenylenediisopropylidene (CAS# 2778-42-9) (TMXDI) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. The company hereby submits a revised, final test plan for this substance. All testing proposed in the previous test plan and/or recommended by the EPA has been completed. Existing plus modeled data now fulfill all Screening Information Set (SIDS) endpoints.

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## 1. Introduction

On November 22, 1999, Cytec Industries Inc. (Cytec) voluntarily agreed to participate in the Environmental Protection Agency's (EPA) High Production Volume Chemical Challenge Program. By participating in this program, Cytec agreed to assess the adequacy of existing data, design and submit test plans to fill data gaps where necessary and appropriate, provide test results, and prepare summaries of the data characterizing each chemical.

The sponsored chemical addressed in this test plan is Isocyanic acid, m-phenylenediisopropylidene (CAS# 2778-42-9) (TMXDI).

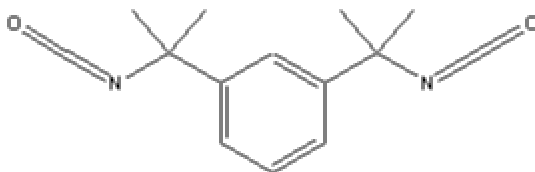
This test plan was first submitted to the Environmental Protection Agency and posted on the EPA HPV Chemical Challenge Program website in October 2002. The test plan was revised in April 2003 in response to EPA comments. A second revision was submitted to EPA in February 2005. Per agreement with the EPA, the sponsors have conducted studies on stability to water (hydrolysis), developmental toxicity and chromosomal aberration to address initial deficiencies of data for these endpoints. These endpoints have now been addressed satisfactorily, and the study robust summaries have been added to the dossier for this chemical. The test plan has been appropriately revised to reflect the newly generated test data, and the dossier, and test plan are now considered final for the purposes of the U.S. HPV Chemical Challenge Program.

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## 2. Designation of Test Substance

The test substance presented in this test plan is Isocyanic acid, m-phenylenediisopropylidene (CAS# 2778-42-9) (TMXDI). Its molecular weight and empirical formula are 244.3 and  $C_{14}H_{16}N_2O_2$ . The chemical structure is as follows:



This substance is known by the following synonyms:

Benzene, 1,3-bis(1-isocyanato-1-methylethyl)-

1,3-Bis(1-isocyanato-1-methylethyl)benzene  
1,3-bis(1-isocyanato-1-methylethyl)benzene  
1,3-Bis(1-isocyanato-1-methylethyl)benzol  
1,3-bis(1-isocianato-1-metiletil)benceno  
1,3-Bis(a-isocyanatoisopropyl) benzene  
m-Bis(1-isocyanato-1-methylethyl)benzene  
Isocyanic acid, a,a,a',a'-tetramethyl-m-xylylene ester  
Isocyanic acid, m-phenylenediisopropylidene ester  
a,a,a',a'-Tetramethyl-m-phenylenedimethylene diisocyanate  
a,a,a',a'-Tetramethyl-m-xylylene diisocyanate  
Tetramethyl-m-xylylene diisocyanate  
TMXDI® (META) aliphatic isocyanate (Trade name)

The material will be referred to as TMXDI in the test plan.

Cytec Industries Inc. has produced in excess of 1 million pounds of this material. As such, there are prescribed conditions for its manufacture, processing, distribution, use and disposal. In general, there is low potential for exposure of humans or the environment. In the work place, potential worker exposure is carefully controlled.

Although diisocyanates are well-known sensitizers, little risk is posed by this chemical. The diisocyanate is manufactured in an essentially closed system with little personnel exposure. Its manufacture is monitored under close technical supervision. Although its vapor pressure is quite low, points of possible exposure are controlled by exhaust systems and, where necessary, carbon filters are used to purify any contaminated air. Protective clothing and respirators are required.

The only worker contact comes from sampling procedures for quality control, and in some instances, during packaging. Exposure would be by skin contact. Inhalation exposure is extremely low due to the use of ventilation and the materials low vapor pressure. Ingestion would not be expected. In customer applications, this material is used at plants by highly experienced personnel well equipped to handle these materials safely.

TMXDI is not sold directly to the consumer market. This material is reacted into the polymers in which they are added, limiting potential exposure in the finished consumer products. Since diisocyanates are well known sensitizers, distribution of this material is restricted to customers that are highly experienced and well equipped to handle material of this kind. As is well known, plants handling isocyanates routinely use exhaust systems to minimize hazards due to contaminated air, and where required, protective clothing and respirators are used. Our choice of customers is restricted to companies well respected in the field and having high standards of industrial hygiene. This material is transported to our customers in drums, totes, or ISO containers by way of truck or ship with little to no risk to the public or the environment. All waste material is drummed and disposed of by approved waste treatment contractors. The material is not regulated as a RCRA hazardous waste.

TMXDI aliphatic isocyanate is a versatile aliphatic isocyanate finding broad end-use applicability. Application areas include specialty coatings, aqueous dispersions, automotive coatings, wood coatings, inks, sealants, adhesives, thermoplastic urethanes, and lacquers.

This chemical imparts improved physical properties to polyurethane products, affording higher strength and improved adhesion, appearance, and flexibility, resulting in more durable products. Common commercial products that may have been made using TMXDI include, fabric and leather finishes, adhesives, automotive paints, printing inks, sealants, and wood coatings. TMXDI poses little to no risk to the end consumer as there is no exposure to TMXDI. In addition to these uses, TMXDI is FDA approved for use in food-packaging under specific listings in the Code of Federal Regulations (CFR) Title 21-Food and Drugs Chapter I-Food and Drug Administration, Department of Health and Human Services.

Table 1. 21 CFR Sanctions

21 CFR	Section	Definition
PART 175—Indirect Food Additives: Adhesives and Components of Coatings-- §175.105 (ADHESIVES)	§175.105	Clears meta-tetramethyl xylene diisocyanate for reaction with one or more of the polyols and polyesters listed in §175.105 and dimethylolpropionic acid and triethylamine, N-methyldiethanolamine, 2-dimethylaminoethanol, 2-dimethyl-amino-2-methyl-1-propanol and/or 2-amino-2-methyl-1-propanol in the production of polyurethane resins intended for use as components of adhesive formulations used in food packaging applications. Cytec Industries Petition Oct. 26, 1993, effective March 12, 1996

### 3. Criteria for Determining Adequacy of Data

All available studies were reviewed and assessed for adequacy according to the standards of Klimisch et al. (1997). Studies receiving a Klimisch rating of 1 or 2 were considered to be adequate. The TMXDI test plan matrix (as shown in Table 2) was constructed after a careful evaluation of all existing data (see Sections 4.1- 4.4.6 below).

The matrix is arranged by study type (columns) and screening data endpoints (rows), and indicates if data are provided for each end point in the set of robust summaries.

Table 2. Test Plan Matrix for TMXDI

<b>CAS No. 2778-42-9</b>	Information	Estimation	Acceptable	New Testing Required
<b>ENDPOINT</b>	Y/N	Y/N	Y/N	Y/N
<b>PHYS/CHEM PROPERTIES</b>				
Melting Point	Y	N	Y	N
Boiling Point	Y	N	Y	N
Density	Y	N	Y	N
Vapor Pressure	Y	N	Y	N
Partition Coefficient	Y	Y	Y	N
Water Solubility	Y	Y	Y	N
<b>ENVIRONMENTAL FATE</b>				
Photodegradation	Y	Y	Y	N
Stability in Water	Y	N	Y	N
Transport between Environmental Compartments (Fugacity)	Y	Y	Y	N
Biodegradation	Y	N	Y	N
<b>ECOTOXICITY</b>				
Acute Toxicity to Fish	Y	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	N	Y	N
Toxicity to Aquatic Plants	Y	N	Y	N
<b>TOXICOLOGICAL DATA</b>				
Acute Toxicity	Y	N	Y	N
Repeated Dose Toxicity	Y	N	Y	N
Genetic Toxicity-Mutation	Y	N	Y	N
Genetic Toxicity-Chromosomal Aberrations	Y	N	Y	N
Toxicity to Reproduction	Y	N	Y	N
Developmental Toxicity	Y	N	Y	N
<b>OTHER TOXICITY DATA</b>				
Skin Irritation (NR)	Y	N	Y	N
Eye Irritation (NR)	Y	N	Y	N
Sensitization (NR)	Y	N	Y	N

Y = yes; N = no

#### 4. Discussion of Available Test Information

##### 4.1 Chemical and Physical Properties

The results of chemical/physical property testing are shown in Table 3.

Table 3. Chemical/physical properties of TMXDI

Endpoint	Value
Melting point (° C)	-10 °C <sup>a</sup>
Boiling point (° C)	292 °C <sup>a</sup>
Vapor pressure (hPa)	0.0043 at 25 °C <sup>a</sup>
Partition coefficient (Log Pow or Kow)	4.74 <sup>b</sup>
Water solubility (mg/l at 25 °C)	5.833 mg/l at 25 °C <sup>b,c</sup>

<sup>a</sup>measured; <sup>b</sup> estimated by EPIWIN; <sup>c</sup>hydrolyzes in water

#### **4.1.1 Melting Point**

A measured melting point of -10 °C has been determined (Achorn et al., 1986).

#### **4.1.2 Boiling Point**

A measured boiling point of 292 °C has been determined (Achorn et al., 1986).

#### **4.1.2 Vapor Pressure**

A measured vapor pressure of 0.0043 hPa at 25 °C has been determined (Achorn et al., 1986).

#### **4.1.4 Octanol/Water Partition Coefficient**

A partition coefficient (Log Pow) of 4.74 has been calculated using the EPIWIN KOWWIN Model Program.

#### **4.1.5 Water Solubility**

A water solubility of 5.833 mg/l at 25 °C has been estimated using EPIWIN WSKOW. As indicated in Section 4.2.2, the test substance hydrolyzes at a rapid rate in water at room temperature, making it impractical to obtain an accurate measured value for water solubility.

#### **4.1.6 Summary/Test Plan for Physical Properties**

Adequate data are available to characterize the physical property endpoints and no testing is needed for these properties.

### **4.2 Environmental Fate/Pathways**

The results of environmental fate modeling and studies are summarized in Table 4 below.

Table 4. Environmental fate parameters for TMXDI

Endpoint	Value
Indirect Photolysis (OH sensitizer) (Hydroxyl Radical Rate Constant) <sup>a</sup> (Atmospheric T <sub>1/2</sub> ) <sup>a</sup>	1.01332 x 10 <sup>-11</sup> cm <sup>3</sup> /(molecule*sec) 12.7 hours
Stability in Water: Half-life (t <sub>1/2</sub> ) <sup>b</sup>	pH = 4: 0.4 hour(s) at 25 °C pH = 7: 0.4 hour(s) at 25 °C pH = 9: 0.3 hour(s) at 25 °C
Henry's Law Constant <sup>a</sup>	3.22 E-6 atm-m <sup>3</sup> /mole (bond estimate)
Environmental transport (Fugacity Level III mass percentages) <sup>a</sup>	Air = 0.779 Water = 18.1 Soil = 62.6 Sediment = 18.5
Biodegradation <sup>b</sup>	Not readily biodegraded

<sup>a</sup> Estimated using EPIWIN

<sup>b</sup> Measured value

#### 4.2.1 Photodegradation

A photodegradation hydroxyl radical rate constant of 1.01332 x 10<sup>-11</sup> cm<sup>3</sup>/(molecule\*sec) and a half-life of 12.7 hours have been estimated using the EPIWIN AOP model program.

#### 4.2.2 Stability in Water

According to an OECD Test Guide-line 111 study, the hydrolysis rate in water at pH 4, 7, and 9 (at 25 °C) is 0.3 – 0.4 hours (Woolley and Mullee, 2003). Hydrolysis was almost instantaneous at pH 1.2 (at 37 °C).

#### 4.2.2 Fugacity

Mass percentages and half-lives in various media were estimated using the EPIWIN Fugacity Model Level III Program. The inputs to the program were the CAS No., measured melting point, boiling point, and vapor pressure. Default emission rates of 1000 kg/hr to air, water and soil were employed.

#### 4.3.4 Biodegradation

An OECD Test Guideline 301D (Close Bottle Test) has been conducted with 2 mg/l of TMXDI (United States Testing Company, Inc., 1988). Degradation after 28-days was determined to be 13.7% as compared to 95% for the aniline reference material. The study was given a reliability rating of 1 (valid without restriction), since it was a guideline study with no restrictions.

#### 4.3.5 Summary/Test Plan for Environmental Fate Parameters

Measured or estimated values are available for photodegradation, hydrolysis in water and environmental transport. The test material photodegrades readily in the atmosphere and

hydrolyzes rapidly in water at pHs 1.2, 4, 7, and 9. Therefore, the material is unlikely to persist in the atmosphere or in aqueous environments. Although the material undergoes some biodegradation after 28 days, it cannot be classified as readily biodegradable.

### 4.3 Ecotoxicity

The results of studies and ECOSAR modeling are summarized in Table 5 below.

Table 5. Ecotoxicity of TMXDI

Endpoint	Value (mg/l)
Toxicity to fish (96-hr LC <sub>50</sub> ) <i>Lepomis macrochirus</i> <i>Pimephales promelas</i>	> 65.88 <sup>a</sup> 0.67 <sup>b</sup>
Toxicity to Daphnia (48-hr LC <sub>50</sub> )	5.2 <sup>b</sup>
Toxicity to Algae (96-hr EC <sub>50</sub> )	2.1 <sup>b</sup>

<sup>a</sup> Based on exposure to water accommodating fraction

<sup>b</sup> Material was dissolved in acetone

#### 4.3.1 Acute Toxicity to Fish

A static, OECD Test Guideline 203 study has been performed in *Lepomis macrochirus* (bluegill sunfish) with TMXDI of approximately 99% purity (Exxon Biomedical Sciences, Inc., 1993). The study was performed using the water accommodating fraction (WAF) of each treatment solution, which was siphoned from the middle portion of the mixing container and divided into 2 replicate chambers. Concentrations of the test material in the WAF were analytically confirmed. The 96 hour no observable effect concentration (NOEC) and LC<sub>50</sub> value were > 52.19 and > 65.88 mg/l, respectively. This study was assigned a reliability rating of 1 (valid without restriction), since it was a guideline study with no restrictions.

The toxicity of TMXDI to *Pimephales promelas* (fathead minnows), was assessed in a static test performed according to USEPA 660/3-75009 guidelines (ABC Laboratories, 1986a). In this study, solubility was aided by dissolving the test material in acetone. The 96 hour NOEC and LC<sub>50</sub> value were 0.32 and 0.67 mg/l, respectively. Mortality, surfacing, loss of equilibrium and/or quiescence were observed at 0.56 and 1.0 mg/l. Since environmental conditions in the study were kept within reasonable limits, the lower LC<sub>50</sub> values (as compared to the previous study) appear to be due to dissolution of the material in acetone. This study was assigned a reliability rating of 1 (valid without restriction), since it was a guideline study with no restrictions.

#### 4.3.2 Acute Toxicity to Aquatic Invertebrates

A static, USEPA guideline study has been performed in *Daphnia magna* with TMXDI (98-99% purity) dissolved in acetone (ABC Laboratories, 1986b). The 48 hour NOEC and

LC<sub>50</sub> value were < 1 and 5.2 mg/l, respectively. This study was assigned a reliability rating of 1 (valid without restriction), since it was a guideline study.

### **4.3.3 Acute Toxicity to Aquatic Plants**

The toxicity of TMXDI (97-98% purity) dissolved in acetone was tested in an OECD Test Guideline 201 study using *Selenastrum capricornutum* algae (United States Testing Company, Inc., 1987). The 96 hour NOEC was 0.34 mg/l and the EC<sub>50</sub> value based on cell growth was 2.1 mg/l. Although the use of the solvent produced a slight "lag" in the growth of control cells, it did not depress the population to a degree severe enough to confound the interpretation of the study. This study was assigned a reliability rating of 1 (valid without restriction), since it was a guideline study with no restrictions.

### **4.3.4 Summary/Test Plan for Ecotoxicity**

LC<sub>50</sub> and EC<sub>50</sub> toxicity values for TMXDI towards fish, Daphnia and green algae have been determined in OECD or EPA guideline studies. The LC<sub>50</sub>/EC<sub>50</sub> values for TMXDI dissolved in acetone are similar in Daphnia and algae (5.2 and 2.1 mg/l, respectively), and are slightly lower in fish (0.67 mg/l). In fish exposed to TMXDI dissolved in the WAF (without acetone), the LC<sub>50</sub> value (> 65.88 mg/l) is orders of magnitude higher than for fish exposed to the material in acetone (0.67 mg/l). No additional testing is necessary.

## **4.4 Human Health Data**

### **4.4.1 Acute Mammalian Toxicity**

This endpoint is filled by an adequate oral toxicity study in Sprague-Dawley rats (Biosphere research Center, 1981a), inhalation studies in Sprague-Dawley rats (Huntingdon Research Centre, 1995) and English smooth-haired guinea pigs (Bio-Research Laboratories, Ltd., 1982), and a dermal toxicity study in New Zealand white rabbits (American Cyanamid Company, 1981a). The oral and dermal LD<sub>50</sub> values (lethal doses in 50% of the animals) were 5 ml/kg (approximately 5350 mg/kg) and > 2000 mg/kg (the only concentration tested), respectively. The LC<sub>50</sub> values for aerosol inhalation were 0.027 mg/l in rats and 0.24 mg/l in guinea pigs. The oral study is considered to be the critical study for the endpoint, and was given a reliability rating of 1 (valid without restriction).

Clinical signs observed in rats treated orally with 2.8 to 7.1 ml/kg TMXDI included diarrhea, crusty material around anus, soft stool, crusty material around face, paws, eyes, nose, and scrotum, cream-colored material around mouth, alopecia, swollen feet, edema around anus, nasal discharge, red-colored nasal discharge, tachypnea, lacrimation, lethargy, urine-soaked fur, piloerection, ataxia, moribundity, cold body temperature, and tremors (Biosphere Research Center, 1981a). The frequency or variety of signs did not appear to increase with increasing doses of test material, and did not exhibit any sex-related trends. The only effects noted in rabbits treated dermally with 2000 mg/kg TMXDI were related to dermal irritation (American Cyanamid Company, 1981a).

In rats exposed to 0.02 - 0.316 mg/l (20 - 316 mg/m<sup>3</sup>) TMXDI aerosol for 4 hours by inhalation, signs of toxicity such as respiratory abnormalities (exaggerated respiratory movements and/or irregular respiration), partial closing of the eyes, a dark appearance of the eyes, reddening of the ears and feet, red/brown staining around the snout and jaws, piloerection, matted and/or wet fur, restless behavior, whole-body hypothermia, immobility, emaciation, a swollen abdomen, lethargy, salivation and weight loss (or reduced weight gain) were observed (Huntingdon Research Centre, 1995). Abnormalities seen in rats that died (all exposed to 0.0935 and 0.316 mg/l and all except one exposed to 0.0533 mg/l) included minimal to marked congestion of the lungs, a swollen appearance of the lungs, a white frothy fluid in the trachea, a fluid-filled thoracic cavity, distension of the gastrointestinal tract with gas, and opacities of the eyes. Minimal to moderate congestion of the lungs was the major finding in rats surviving to study termination (all exposed to 0.02 mg/l and one exposed to 0.0533 mg/l).

In guinea pigs exposed to 0.195 – 0.457 mg/l TMXDI aerosol for 1 hour by inhalation, clinical signs observed during the first three days after exposure consisted of weakness, lethargy, gasping/rales, weight loss and discharge from eyes, nose or mouth (Bio-Research Laboratories, Ltd., 1982). Gross pathology revealed swollen, reddened, rubbery lungs and lung congestion in animals that died (all exposed to 0.457 mg/l, all males exposed to 0.355 mg/l and 1-3 per group in the other groups). Swelling, reddening, increased consistency, collapse and foci of discoloration were observed at termination in survivors.

#### **4.4.2 Repeated Dose Mammalian Toxicity**

A 90-day inhalation toxicity test (6 hours/day, 5 days per week for 13 weeks) with 0.4, 0.8, or 1.6 ppm (4, 8 or 16 mg/m<sup>3</sup>) TMXDI vapor (98 % pure) has been performed in Sprague-Dawley rats and CD-1 mice (Bushy Run Research Center, 1990). A no observable adverse effect level (NOAEL) was not established in either species, since evidence of toxicity occurred at all exposure concentrations. Exposure 1.6 ppm TMXDI was associated with increased mortality and depressed weight gain in rats and mice. The mortality rate of mice exposed to 0.8 ppm (but not rats) also was increased. Respiratory difficulties (e.g. gasping, audible respiration, etc.) were observed in rats and mice exposed to 0.8 or 1.6 ppm. Reddening of the ears and paws (which occurred in all exposed groups) was most noticeable during exposure and appeared to be concentration-related. Blepharospasm and alopecia were also observed in mice exposed to 0.8 or 1.6 ppm. The alopecia was prominent during the first several weeks of exposure and in some cases resulted in nearly total hair loss. However, mice regenerated new hair during the remainder of the study. For rats and mice which died on study, histopathologic lesions generally occurred throughout the entire respiratory tract. Rhinitis and squamous metaplasia also were noted in the nasal cavities of rats and mice exposed to 0.4 ppm. There was no effect of treatment on the histology of any reproductive organ examined. This study was assigned a reliability rating of 1 (valid without restriction), and is considered to be the critical study for the endpoint.

A 28-day week inhalation toxicity test (6 hours/day, 5 days per week for 4 weeks) with 0.38, 1.5, and 4.4 mg/m<sup>3</sup> TMXDI aerosol (98 % pure) also has been performed in Sprague-Dawley rats (Bushy Run Research Center, 1988). The NOAEL assigned to the study was 1.5 mg/m<sup>3</sup>. Body weights and lung to body weight ratios tended to decrease and increase (respectively) in animals exposed to 4.4 mg/m<sup>3</sup>, but were not significantly different from control. Gross portmortem

evaluations showed evidence of discolored lungs in four of five males exposed to 4.4 mg/m<sup>3</sup>. Microscopically, subacute/chronic inflammation of the lungs and hyperplastic/metaplastic changes of the bronchi occurred in high-dose animals. These changes were not seen in animals from the control or the two lower exposure levels.

Results of the OECD Test Guideline 421 study that was recently conducted (see Section 4.4.4) indicate that repeated, oral exposure of up to 150 mg/kg bw/day TMXDI for 19 days or 40-41 days is well-tolerated in male and female rats (respectively) (Safepharm Laboratories Limited, 2005). While general irritant type effects were seen at this dose, they were not indicative of systemic toxicity and were not associated with an adverse effect on body weight gain. Exposure to the highest concentration tested (250 mg/kg bw/day) was associated with a reduction in body weight gain and food consumption of males and females. However, no treatment-related histopathological changes were observed in any of the organs that were examined (coagulating glands, epididymides, prostate, seminal vesicles, testes, pituitary, ovaries, uterus/cervix, or vagina) from animals exposed to this concentration.

### **4.4.3 Genetic Toxicity**

#### **4.4.3.1 Mutagenicity**

TMXDI (approximately 98% pure) has been tested for mutagenicity in a standard Ames assay conducted with *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 (Bushy Run Research Center, 1986). The material was dissolved in acetone prior to use. In the assay, the highest concentration of TMXDI that did not cause excessive toxicity (30 micrograms/plate) was not mutagenic in the absence or presence of a metabolic activation system. This study was assigned a reliability rating of 1 (valid without restriction), since it was conducted according to GLP and was described in sufficient detail.

#### **4.4.3.2 Chromosomal Aberration**

An OECD Test Guideline 473 chromosomal aberration test was performed in Chinese Hamster Ovary (CHO) cells with concentrations of TMXDI ranging from 0 - 40 micrograms/ml without S9 and 0 - 20 micrograms/ml with S9 from rat liver induced with phenobarbitone and beta-naphthoflavone (Safepharm Laboratories Limited, 2003). The material was dissolved in dimethylsulfoxide (DMSO) prior to use. Two experiments were conducted with either a 4 hour treatment period (followed by a 20 hour recovery period) or a 24 hour treatment period. In both experiments, there was no effect of test material on the frequency of cells with aberrations at any dose level, in either the presence or absence of S9 mix. This study was assigned a reliability rating of 1 (valid without restriction), since it was conducted according to an established guideline.

### **4.4.4 Reproductive and Developmental Toxicity**

In the OECD Test Guideline 421 study, Sprague Dawley rats (10/sex/dose) were given 0, 15, 150 or 250 mg/kg bw/day TMXDI in arachis oil for 14 days prior to mating (males and females), up to 14 days during mating (males and females), during gestation (females only), and to day 5 of

lactation (females only) (Safepharma Laboratories Limited, 2005). The NOAELs for systemic, reproductive and developmental toxicity were 150 (see Section 4.4.2), 250 and 250 mg/kg bw/day. Both testes and epididymis weights of all treated groups were greater than control. However, this was due to one control male with small testes and epididymides and was not considered to be treatment-related. There was no significant effect of test material on histopathology of reproductive organs or any index of fertility measured. There also was no significant effect of treatment on any index of toxicity measured in pups (live birth or viability index, litter size, litter weight, pinna unfolding, surface righting reflex, sex ratio or gross pathology). In the high dose group, there was a significantly lower mean pup weight on Days 1 and 4 of lactation. There was a concomitant reduction in mean total litter weight compared to control values. This was thought to be due to higher than normal mean offspring weights of controls and was not considered to be related to treatment. There was no effect of treatment with 150 or 15 mg/kg bw/day on pup body weight. This guideline study was assigned a reliability rating of 1 (valid without restriction), and is considered to be the critical study for the endpoint.

Results of the 90-day repeated dose inhalation study indicate that inhalation of up to 1.6 ppm (16 mg/m<sup>3</sup>) TMXDI has no effect on the histopathology of the cervix, vagina, ovaries, vulva, oviduct, urethra, uterus, mammary glands (both sexes), prostate, testes, penis, epididymides, ureter, coagulating gland, or seminal vesicles of rats or mice (Bushy Run Research Center, 1990). This also suggests that the material has no effect on reproduction at this concentration.

#### **4.4.5 Additional Data**

##### **4.4.5.1 Skin and Eye Irritation**

Adequate studies in rabbits show that TMXDI is moderately irritating to skin and slightly irritating to eyes (Biosphere Research Center, 1981b; American Cyanamid Company, 1981b). Effects observed in the skin irritation study included slight to severe erythema and eschar formation and slight edema. Eye irritation was limited to the conjunctiva (discharge, chemosis and redness). Rinsing with water lessened, but did not totally eliminate eye irritation. Both studies described above were assigned reliability ratings of 1 (valid without restriction) because they were conducted according to generally accepted scientific standards and are described in sufficient detail.

##### **4.4.5.2 Sensitization**

Results of a well-conducted, GLP study in guinea pigs indicate that TMXDI is a sensitizer (Biosphere Research Center, 1981c). Animals receiving induction applications of 0.36 M TMXDI in olive oil exhibited a dermal contact sensitization response when challenged five days later with the same concentration of test material. However, evidence of sensitization was negligible upon rechallenge. An additional GLP study shows that when applied intradermally, a concentration of 0.0333% TMXDI/Guinea Pig Serum Albumin (GPSA) does not cause immediate hypersensitivity in guinea pigs (Bio-Research Laboratories, Ltd., 1984).

The ability of TMXDI to cause respiratory sensitization in guinea pigs also has been tested according to GLP (Bio-Research Laboratories, Ltd., 1984). In this study, twelve guinea pigs were exposed for 3 hours on study days 1 - 5 to an aerosol of TMXDI at a target concentration of

36 micrograms/l. On study days 22, 23 and 26, animals were exposed to an aerosol of TMXDI/GPSA at a concentration of 15-20 micrograms/l for a 20-minute period. Evidence of irritation (nasal and oral discharge) occurred during induction, but an increase in respiratory rate equal to or greater than 36% (the threshold value for a positive response) did not occur. Therefore, there was no evidence of sensitization.

The sensitization studies described above were assigned reliability ratings of 1 (valid without restriction) because they were conducted according to generally accepted scientific standards and are described in sufficient detail.

#### **4.4.6 Summary/Test plan for Mammalian Toxicity**

Adequate studies with TMXDI have been conducted for all endpoints. Acute oral and dermal exposure to fairly large amounts of TMXDI is required to cause lethality. Acute inhalation exposure to concentrations = 0.02 mg/l causes lethality in rats. Symptoms of toxicity observed in animals exposed to nonlethal concentrations of TMXDI are consistent with its ability to cause irritation to the skin, eyes and respiratory tract. Well-conducted studies in guinea pigs show that TMXDI is a dermal sensitizer. However, the material does not cause immediate hypersensitivity or respiratory sensitization. Results of the 90-day repeated dose inhalation study in rats and mice show that exposure to = 4 mg/m<sup>3</sup> TMXDI causes respiratory irritation and inflammation. An OECD Test Guideline 421 study in rats indicates that oral exposure of up to 250 mg/kg bw/day TMXDI (a systemically toxic dose) prior to mating and during gestation and lactation did not cause reproductive or developmental toxicity. Adequate studies show that TMXDI is not mutagenic or clastogenic.

### **5. Summary**

In summary, valid data are present to satisfy all physical/chemistry, environmental and mammalian toxicity endpoints. Existing and new studies on acute, repeated dose, genetic (mutations and chromosomal aberrations) and reproductive/developmental toxicity are sufficient to satisfy these endpoints. Data for eye and skin irritation and sensitization are adequate (although not required).

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